

Emphysematous pyelonephritis: A 10-year experience with 26 cases

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ABSTRACT

Background: Emphysematous pyelonephritis (EPN) is a necrotizing infection which results in gas within the renal parenchyma, collecting system, or perinephric tissue. A majority of cases occur in patients with diabetes mellitus (DM). In EPN, early aggressive medical treatment may avoid nephrectomy. **Aims:** The aim of this study was to analyze the characteristics of patients with EPN with respect to patient demographics, clinical presentation, diagnostic investigations, microbiological findings, treatment modality and outcome, and the influence of prognostic factors on the outcome. **Materials and Methods:** We reviewed the hospital records of 26 patients with EPN for clinical, laboratory, radiological, and microbiological findings, treatments given, and outcome. The severity of EPN was graded as per the Huang classification. We applied the reported prognostic factors to our patients to find out whether these factors correlated with failure of conservative treatment. **Results:** All the study subjects had DM and all but two of them were females. The majority of our patients (61.5%) had extensive EPN (class 3 or 4) and majority (76.9%) had two or more bad prognostic factors. *Escherichia coli* was the most common causative organism involved in 50% of our cases. Twenty-three (88.5%) of our patients responded to conservative treatment, two required nephrectomy, and one expired on conservative treatment. **Conclusions:** In this series of patients with EPN, all had DM, nearly all were women, and *E. coli* was the most frequently isolated pathogen. Nearly a third of our patients had bilateral disease. Despite the presence of two or more bad prognostic factors and extensive EPN (class 3 or 4) in a majority of our patients, conservative treatment afforded a striking success rate of 88.5%. We recommend early aggressive medical treatment and suggest that nephrectomy should be considered only if patients deteriorate or do not improve on conservative treatment.

Key words: Conservative treatment, diabetes mellitus, emphysematous pyelonephritis, gas-forming infection, necrotizing pyelonephritis

INTRODUCTION

Infections remain a major cause of morbidity and mortality in patients with diabetes in developing countries.^[1] Emphysematous pyelonephritis (EPN) is an uncommon acute necrotizing infection of the renal parenchyma and perirenal tissue, which results in gas within the renal

parenchyma, collecting system, or perinephric tissue.^[2-3] More than 90% of all cases of EPN occur in patients with diabetes mellitus (DM).^[4,5] In the literature, the first case of EPN was reported by Kelly and MacCallum in 1898.^[6] Over half a century later, the term “emphysematous pyelonephritis” was recommended by Schultz and Klorfein because of its emphasis on the relationship between the gas formation and the nature of the infectious process.^[7] EPN is a life-threatening infection with a mortality rate as high as 80% in earlier studies.^[4,5] In this study, we analyzed the characteristics of 26 patients with EPN with respect to patient demographics, clinical presentation,

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diagnostic investigations, microbiological findings, treatment modality and outcome, and the influence of prognostic factors on the outcome.

MATERIALS AND METHODS

The study was carried out in the Department of Endocrinology at Sher-i-Kashmir Institute of Medical Sciences, Srinagar, Kashmir, which is the only tertiary care hospital of Kashmir valley and is a 750-bedded hospital. The study involved 26 consecutive diagnosed cases of EPN admitted during the period 2004 to 2014. The diagnosis of EPN was based on clinical features and documentation of gas within the renal parenchyma, collecting system, or perinephric tissue on computed tomography (CT) of abdomen. We retrospectively reviewed the clinical, laboratory, radiological, and microbiological findings, treatment modality, and outcome of these patients. The severity of EPN was graded as per the Huang classification. According to this classification, class 1 EPN is defined as gas in the collecting system only, class 2 as gas in the renal parenchyma with no extension to the extrarenal space, class 3A as extension of gas or abscess to the perinephric space, class 3 B as extension of gas or abscess to the pararenal space, and class 4 as bilateral EPN or EPN in a solitary kidney.^[8] Certain factors have been associated with poor outcome in EPN; these bad prognostic factors include thrombocytopenia, azotemia, hematuria, altered consciousness, shock (systolic blood pressure [BP] <90 mmHg) on initial presentation, severe proteinuria, need for emergency hemodialysis, severe hypoalbuminemia (serum albumin <3 g/dl), polymicrobial infections, and extension of infection to the perinephric space.^[3,8-11] We applied these reported prognostic factors to our patients and tried to find out whether these factors correlated with failure of conservative treatment.

We defined conservative treatment of EPN as medical treatment alone or a combination of medical treatment and percutaneous catheter drainage. The success of conservative treatment was defined as clinical resolution and disappearance/decrease in gas on follow-up imaging during hospitalization and after discharge from hospital. As per the protocol followed at our department, the treatment included early adequate fluid resuscitation, rapid control of glycemia through insulin infusion, close clinical and biochemical monitoring, electrolyte management, initiation of two potent antibiotics at diagnosis, and percutaneous catheter drainage (if required). The antibiotics included a third-generation cephalosporin and a fluoroquinolone; patients who had septic shock received vancomycin and imipenem. The antibiotics were revised if indicated by the results of susceptibility testing of the isolated organism.

Cases in whom candida species were isolated were managed with amphotericin B deoxycholate for 2 weeks followed by oral fluconazole for 2 weeks. Deterioration on this protocol led to consideration for nephrectomy in two patients. All patients were followed up for at least 6 months after discharge from the hospital and consented for publication of their data; for the single patient who died, consent was provided by her son. The study was approved by the Institutional Ethical Committee. Results are expressed as mean \pm standard deviation.

RESULTS

Clinical data

The baseline characteristics of the 26 study subjects are shown in Table 1. All but two of the subjects were females. The subjects had a mean age of 49 ± 1.3 years (range 20–70 years). All the study subjects had DM (23 type 2 and 3 type 1); the mean duration of diabetes was 6.8 ± 5.3 years and two patients had their DM diagnosed during the episode of EPN. Four patients including two with type 2 diabetes had diabetic ketoacidosis while four others had nonketotic hyperosmolar state. Two patients had renal stones, one of whom had grade III hydronephrosis.

The clinical and laboratory characteristics of the patients are shown in Table 2. The median duration of symptoms before diagnosis was 9 days with a range of 1–30 days. The prominent clinical manifestations included fever/chills (92.3%), flank pain (88.5%), renal angle tenderness (76.9%), vomiting (50%), and dysuria (50%). Three patients had palpably enlarged kidney and two other patients had crepitus in the lumbar region. Seven (26.9%) patients had hypotension at admission and seven (26.9%) patients had altered sensorium. Nine (34.6%) patients had had recurrent urinary infections in the past.

Laboratory and radiological data

All patients had pyuria and more than a quarter (26.9%) had hematuria. A majority (84.6%) of patients had leukocytosis

Table 1: Baseline characteristics of patients

Characteristic	n (%) patients
Age (years)*	49 (1.3)
Female	24 (92.3)
DM	26 (100)
DKA	4 (15.3)
NKHS	4 (15.3)
Duration of DM (years)*	6.8 (5.3)
Diabetic neuropathy	18 (69.2)
Diabetic nephropathy	11 (42.3)
Diabetic retinopathy	7 (26.9)
Renal stones	2 (7.6)
Obstructive uropathy	1 (3.8)

*Data are expressed as mean (SD). DKA: Diabetic ketoacidosis, NKHS: Nonketotic hyperosmolar state, DM: Diabetes mellitus, SD: Standard deviation

and over a third (34.6%) had thrombocytopenia; the mean total leukocyte count of the patients was 15,470/mm³ with a range of 3500–27,770/mm³. The blood glucose concentration at admission ranged from 224 to 860 mg/dl with a mean of 450 ± 154 mg/dl; the mean glycated hemoglobin (HbA1c) at diagnosis of EPN was 10.7 ± 2.4% and ranged from 6.4 to 16% reflecting a poor glycemic control in majority of the patients. More than three-fourths (76.9%) of the patients had azotemia at presentation; the mean serum creatinine was 2.14 ± 0.9 mg/dl with a range of 0.9–4.7 mg/dl. Sixteen patients had severe hypoalbuminemia (serum albumin <3 g/dl). All patients had ultrasonography and CT of abdomen; while the former was diagnostic in 73.1%, the latter revealed the diagnosis in all. The left kidney

was involved in 10, the right in 8, and both kidneys in 8 patients. We classified our patients on the basis of Huang classification with three (11.5%) in class 1, seven (26.9%) in class 2, four (15.3%) in class 3A, four (15.3%) in class 3B [Figure 1], and 8 (30.8%) in class 4 [Figure 2]. Of 26 patients, 20 (76.9%) had two or more bad prognostic factors [Table 3].

Microbiologic data

Escherichia coli was the most commonly isolated organism and was isolated in a total of 13 patients (from blood and urine in 6, urine alone in 4, and pus alone in 3). *Proteus mirabilis* was isolated from urine in two patients. In two patients, we isolated candida species from urine. Polymicrobial infection was documented in one patient (*Klebsiella pneumoniae* was isolated from urine and *Pseudomonas aeruginosa* from blood). Acinetobacter was isolated from urine in one patient. No organism was isolated from any sample in 7 (26.9%) patients.

Outcome

Of the 26 patients in our series, 17 were managed with medical treatment alone, 7 with a combination of medical treatment and percutaneous catheter drainage, and only two patients underwent nephrectomy and both of them survived. The first patient was a 42-year-old female with type 2 DM and chronic liver disease who presented with class 3A EPN and initial CT abdomen had shown more than 50% renal parenchymal destruction. She deteriorated on conservative treatment and repeat CT revealed worsening of renal parenchymal destruction which prompted the decision to subject her to nephrectomy 5 days after admission. The second patient was a 70-year-old female

Table 2: Clinical and laboratory characteristics of patients

Variable	n (%) patients
Clinical features	
Fever/chills	24 (92.3)
Flank pain	23 (88.5)
Vomiting	13 (50)
Dysuria	13 (50)
Renal angle tenderness	20 (76.9)
Palpable kidney	3 (11.5)
Altered sensorium	7 (26.9)
Hypotension (systolic BP <90 mmHg)	7 (26.9)
Laboratory findings	
Pyuria	26 (100)
Leukocytosis (leukocyte count >10,000/mm ³)	22 (84.6)
Leukocyte count/mm ³ *	15,470 (5640)
Hematuria	7 (26.9)
Thrombocytopenia (platelet count <120,000/mm ³)	9 (34.6)
Acute renal failure	20 (76.9)
Serum creatinine (mg/dl)*	2.14 (0.91)
Severe hypoalbuminemia (<3 g/dl)	16 (61.53)
HbA1c %*	10.7 (2.4)
Blood glucose at admission* (mg/dl)	450 (154)
Side	
Left	10 (38.5)
Right	8 (30.8)
Bilateral	8 (30.8)
CT class	
Class 1	3 (11.5)
Class 2	7 (26.9)
Class 3a	4 (15.3)
Class 3b	4 (15.3)
Class 4	8 (30.8)

*Data are expressed as mean (SD). SD: Standard deviation, BP: Blood pressure, HbA1c: Glycated hemoglobin

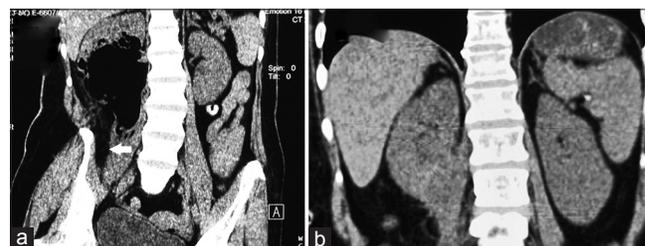


Figure 1: (a) Computed tomography showing the right kidney replaced by the gas and extension of gas to the right psoas muscle (white arrow) (class 3B emphysematous pyelonephritis); (b) disappearance of gas 4 weeks after initiation of treatment

Table 3: The computed tomography class, prognostic factors, treatment, and outcome

Computed tomography class	Bad prognostic factors	Treatment			Outcome	
		Medical alone	Medical and PCD*	Nephrectomy	Survived	Death
1 and 2 (n=10)	<2 (n=6)	5	1	0	6	0
	≥2 (n=4)	3	1	0	4	0
3 and 4 (n=16)	<2 (n=0)	0	0	0	0	0
	≥2 (n=16)	9	5	2	15	1

*PCD: Percutaneous catheter drainage

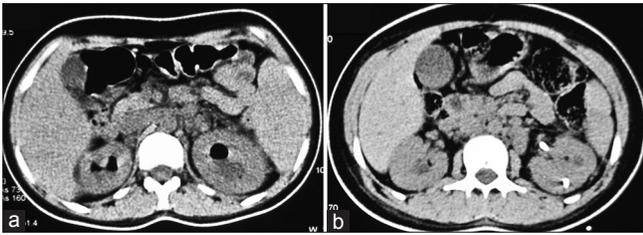


Figure 2: (a) Computed tomography showing diffusely enlarged kidneys and gas in the kidneys bilaterally, indicative of bilateral emphysematous pyelonephritis (class 4 emphysematous pyelonephritis); (b) disappearance of gas 4 weeks after initiation of treatment

with complicated type 2 DM who presented with class 3B EPN, sepsis and multiple organ dysfunction. Her initial treatment included antibiotics (vancomycin and imipenem), inotropic support, supportive care, and peritoneal dialysis. Lack of clinical and biochemical improvement led to emergency nephrectomy 4 days after admission.

There was a single death involving a 70-year-old female who, in addition to bilateral EPN, had comorbidities including myelodysplastic syndrome and obstructive uropathy. The conservative treatment in our series had a very impressive (88.5%) success rate succeeding in 23 of the 26 patients.

DISCUSSION

EPN is an uncommon necrotizing infection predominantly seen in patients with diabetes. All our patients were diabetic. EPN is a disease in women with a female:male ratio of 3:1.^[9] In our series, the female dominance was even more striking (12:1) than in other series. The increased occurrence in women is presumably because of their increased susceptibility to urinary tract infection.^[2] The only exception to this female predominance is that males undergoing renal transplantation are more likely to suffer.^[12] The most common clinical features in our series and reported by others include fever/chills, flank pain, renal angle tenderness, vomiting, and dysuria. These symptoms and signs are nonspecific and cannot differentiate EPN from the usual pyelonephritis. Crepitus in the lumbar region, though exceedingly rare, can provide an important clinical clue to the presence of EPN. Only two ($\approx 8\%$) of our patients had crepitus in the lumbar region. Given the absence of any signs or symptoms specific to this condition, poor response to antibiotic treatment in a patient with DM thought to have uncomplicated pyelonephritis should immediately arouse suspicion of this life-threatening infection and prompt an early CT abdomen to clinch the diagnosis and plan treatment.

The factors believed to underlie the pathogenesis of EPN include gas-forming bacteria, high tissue glucose

concentrations, impaired tissue perfusion, and defective immune response which occurs in DM.^[13] The high tissue glucose level acts as a substrate for the microorganisms such as *Enterobacteriaceae* to produce hydrogen (H_2) and carbon dioxide (CO_2) by mixed acid fermentation of glucose. In a study by Huang *et al.*, five of the six gas samples contained H_2 and all the gas samples contained CO_2 .^[8] Our patients had had poor glycemic control before getting EPN as reflected by high average HbA1c. Apart from DM, our patients had no significant predisposing factors such as obstructive uropathy for the development of EPN. In our series, renal stones were present only in two patients causing obstructive uropathy in one patient.

E. coli is by far the most common causative organism for EPN isolated in 47–90% of the patients; the other commonly involved organisms include *P. mirabilis*, *K. pneumoniae*, *Enterococcus* species, and *P. aeruginosa*.^[3,10,11] In keeping with the literature, we also found that *E. coli* to be involved in 50% of our cases and *P. mirabilis* to be the second most frequently isolated pathogen. In our series, *Candida albicans* was the causative organism in two patients. *C. albicans* has been occasionally identified as a pathogen in EPN.^[3,14] *Acinetobacter* was isolated from urine in one patient. In our study, seven patients (26.9%) were culture-negative in both urine and blood.

In EPN, left kidney is more frequently involved than the right. A recent meta-analysis has reported that 52% of patients had left-sided, 37.7% right-sided, and 10.2% bilateral EPN.^[10] Huang *et al.* have reported that 67, 25, and 8% of the 48 patients with EPN had left sided, right sided, and bilateral disease, respectively.^[8] In our series, the left kidney was involved in 38.5% patients and the right kidney was involved in 30.8% patients. In the literature, bilateral EPN is reported to occur in up to 10% of patients.^[15] In our series, a much larger proportion of patients (30.8%) had bilateral EPN. To the best of our knowledge, this is the highest reported percentage of bilateral involvement in patients with EPN.

Some studies have focused on the factors that are associated with poor outcome in EPN. Wan and Rullard reported that thrombocytopenia, azotemia, and hematuria were predictors of poor outcome in EPN.^[9] Huang *et al.* have reported that initial presentations of thrombocytopenia, altered consciousness, severe proteinuria, shock (systolic BP <90 mmHg), and extension of infection to the perinephric space are significantly associated with mortality.^[8] A recent meta-analysis has reported that in patients with EPN, shock is associated with high mortality rate.^[10] Another recent study has reported that need for emergency hemodialysis, severe hypoalbuminemia (serum

albumin <3 g/dl), and polymicrobial infections are bad prognostic factors in patients with EPN.^[11] In a study of 21 patients with EPN, it was reported that only hematuria is associated with bad prognosis.^[3] An Indian study by Kapoor *et al.* reported that altered mental status, thrombocytopenia, renal failure, and severe hyponatremia at presentation are associated with higher mortality rates whereas extensive renal parenchymal destruction is associated with a need for nephrectomy.^[16]

Of our 26 patients, 20 (76.9%) had 2 or more bad prognostic factors. In our series, 16 patients had extensive EPN (class 3 or 4) and all these patients had ≥ 2 bad prognostic factors [Table 3]. Of these 16 patients, conservative treatment was successful in 13 patients and unsuccessful in 3 patients (2 needed nephrectomy and 1 died). Huang *et al.* in a study of 48 cases concluded that nephrectomy can provide the best management and should be promptly attempted for extensive EPN with a fulminant course (≥ 2 bad prognostic factors).^[8] Our findings seriously question this radical approach as 13 of our 16 patients with extensive (class 3 or 4) EPN responded to conservative treatment. Similar results have been reported by Lu *et al.*^[11] It is supposed that high tissue glucose levels may cause a fulminant course in patients with DM because it can provide gas forming microbes with a microenvironment more favorable for growth and catabolism.^[3,17] In our series, glycemic control had no prognostic significance as all but one of our patients despite having poor glycemic control as reflected by their high mean HbA1c of $10.7 \pm 2.4\%$ recovered. Similarly, other studies have concluded that glycemic control is not a prognostic factor in patients with EPN.^[9-11]

The treatment of EPN is controversial. Traditionally, early nephrectomy has been considered the treatment of choice in EPN with few reports suggesting increased mortality with medical therapy as compared to surgery.^[18,19] However, surgery is often poorly tolerated in EPN due to poor hemodynamic status; the mortality rate in a series by Ahlering *et al.* advocating emergency nephrectomy was 42%.^[20] Kapoor *et al.* have also reported that early nephrectomy is associated with higher mortality rates than an initial conservative approach.^[16] In 1996, Chen *et al.* reported that antibiotic therapy combined with CT-guided percutaneous drainage was an acceptable alternative to nephrectomy.^[21] In that study, most patients received medical and percutaneous therapy and only two patients required nephrectomy. The treatment of EPN has evolved over the years from invasive surgery to more conservative approaches due to the availability of better imaging modalities, potent antibiotics, and image-guided drainage. Over the last two decades, improvements in management

techniques have drastically reduced the mortality rate of EPN to 21%.^[22,23] A recent meta-analysis has shown that compared to emergency nephrectomy, percutaneous drainage and medical management alone are associated with a significantly lower mortality rate.^[10] Our results also reflect the evolving trends in the management of EPN as the success rate of conservative treatment in our series was 88.5%.

About a third (8/26) of our patients had bilateral EPN. Nephrectomy in such patients would obviously necessitate lifelong renal replacement therapy. Successful nonsurgical management of bilateral EPN has been previously reported by us and others.^[24-29] Seven of our 8 patients with bilateral EPN responded to medical treatment alone (5 patients) or a combination of medical treatment and percutaneous catheter drainage (2 patients) while one patient expired.

The likely reasons for the remarkably low mortality (<4%) in our series are rapid glycemic control, early and aggressive fluid resuscitation, use of a combination of two potent antibiotics, and in the vast majority, absence of additional risk factors other than DM for the development of EPN.

CONCLUSION

In this series of patients with EPN, all had DM, nearly all were women, and *E. coli* was the most frequently isolated pathogen. Nearly a third of our patients had bilateral disease. Despite the presence of two or more bad prognostic factors and extensive EPN (class 3 or 4) in a majority of our patients, conservative treatment afforded a striking success rate of 88.5% with only two patients requiring nephrectomy and one patient succumbing on conservative treatment. We recommend early aggressive medical treatment and suggest that nephrectomy be considered only if patients deteriorate or do not improve on conservative treatment.

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Conflicts of interest

There are no conflicts of interest.

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